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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,423	07/31/2003	Masaya Tohyama	59150-8023.US00	3705

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,423	TOHYAMA ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/14/07, 6/12/07.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 21,22,24-27 and 263-266 is/are pending in the application.

4a) Of the above claim(s) 24 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 21,22,25-27 and 263-266 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 21,22,24-27 and 263-266 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 14 May 2007 and 12 June 2007 have been entered. Claims 21 – 22, 24 – 27, and 263 – 266 are pending.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 14 May 2007 has been entered.

Election/Restrictions

3. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 25 July 2005.

4. Claims 21 – 22, 25 – 27, and 263 – 266 are pending and under examination.

Priority

5. Applicant is reminded that for the purposes of applying prior art, the effective filing date of all claims under examination is 30 April 2003. The reasons why this is the effective filing date were set forth at pp. 2 – 3 of the office action mailed 12 March 2007. Applicant did not traverse the examiner's determination that this is the appropriate effective filing date for these claims.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection stands for the reasons of record and explained in further detail below. The claims have been amended to encompass compositions comprising a protein that either has the sequence of SEQ ID NO:2, also called Pep5, or is at least 90% identical thereto "which retains the biological activity of Pep5". It is without question that the specification describes SEQ ID NO:2, an amino acid sequence which is 15 residues long. The specification also discloses a single mutant wherein one amino acid is added to one end of SEQ ID NO:2. This protein is over 90% identical to SEQ ID NO:2 and has one of the biological activities of SEQ ID NO:2. The specification discloses, at p. 346 lines 9 – 26 and p. 353 lines 24 – 30, that both SEQ ID NO:2 and SEQ ID NO:2 with an additional C-terminal alanine are effective in inducing nerve regeneration. Claims to proteins at least 90% identical to SEQ ID NO:2 which induce nerve regeneration might be considered described, as applicant clearly shows possession of two members of this genus.

However, applicant has provided a broad expansive definition of "biological activity" at p. 87 lines 6 – 31. Clearly applicant considers "biological activity" to be very expansive, and is "not limited to, for example, an interaction with an antibody... and the like" (p. 172 second paragraph). The definitions of "biological activity" are so broad as to include any and all possible biological functions of the sequence. The specification fails to show a correlation between the structures disclosed and the "biological activity" as broadly defined. In order to provide evidence of possession of a genus, such as those starting materials for the claimed methods which all have the recited "biological activity", the specification must disclose to the public those structural elements common to all members of the genus claimed. See Synopsis of Application of Written Description Guidelines, available at http://www.uspto.gov/web/menu/written.pdf, particularly p. 9. Here, applicant has not described those structures which impart "biological activity" as claimed and as defined in the specification. Clearly, applicant was not in possession of the full genus of protein sequences which are encompassed by claims 21 and 27. As the specification does not provide evidence of possession of the compounds claimed, the written description requirement is not satisfied.

Applicant argues, at pp. 4 – 5 of the remarks filed 14 May 2007, that the specification provides examples of assays one could perform to determine if Rho activity is maintained, among certain other biological activities. While the specification does in fact describe such

assays, the claims are not limited to proteins which turn up positive in these assays. Rather, they are drawn to administration of proteins with "biological activity", which is defined much more broadly than the activity measured in these particular assays. While it is certainly within the skill of the artisan to perform the cited assays, description of the assays does not provide written description support for the claimed genus of proteins 90% identical to SEQ ID NO:2 with "the biological activity of Pep5" as claimed.

7. Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a protein at least 90% identical to SEQ ID NO:2 wherein the protein regenerates nerves, does not reasonably provide enablement for compositions comprising proteins at least 90% identical wherein the protein "retains the biological activity of Pep5" as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection stands for the reasons of record. Briefly, the specification shows actual reduction to practice of two proteins within the scope of the claims, namely SEQ ID NO:2 itself and SEQ ID NO:2 with a C-terminal alanine. The specification shows both how to make the proteins and how to use them, as they both are able to functionally regenerate nerves. However, what is claimed is considerably broader than this, even given that the claims have been narrowed to require 90% identity to SEQ ID NO:2. The specification discloses no substitution or deletion variants which retain any particular activity. There is no indication as to what regions of the proteins must be retained such that "biological activity", as broadly defined at pp. 87 and 172, is maintained. Furthermore, while the specification discloses how to use SEQ ID NO:2 with or without a C-terminal alanine (i.e. for nerve regeneration), the specification does not disclose how to use any protein with "biological activity" as broadly defined. The intended use of the compositions of claims 21 and 27 is for regenerating nerves, but the claims encompass proteins with any biological activity, no matter whether it is related to nerve regeneration or not.

As set forth previously, Rudinger teaches that random mutations within a protein sequence would be expected to alter the function of a protein. Thus the prior art indicates that many of the proteins which are at least 90% identical to SEQ ID NO:2 would be expected to be

nonfunctional in the nerve regeneration assays. The specification fails to disclose to the skilled artisan how to use those variants which are at least 90% identical to SEQ ID NO:2 but which fail to regenerate neurons. The scope of independent claims 21 and 27 therefore encompasses an unreasonably large number of variants for which enablement has not been demonstrated and for which it would not reasonably be expected, given the paucity of guidance and working examples beyond those related to nerve regeneration. Thus to be able to both make and use the full scope of the invention of claims 21 and 27, the skilled artisan would have to undertake a great deal of experimentation in order to discover how to use these variants which do not regenerate nerves. Given the state of the art, the complex nature of the invention, and the lack of guidance commensurate in scope with the full breadth of "biological activity", the large degree of experimentation required would clearly be undue. Amendment to "...90% identical thereto, which regenerates nerves" may be sufficient to overcome this rejection.

Applicant argues, at pp. 5 – 6 of the remarks filed 14 May 2007, that it is within the skill of one in the art to determine if the variants "retain the biological activity of Pep5", and that such experimentation would be routine, not undue. The examiner agrees that it is within the skill of the artisan to make and test variants, but 35 USC 112 first paragraph requires that the specification set forth how to make and use, not make and test, the invention. The invention of independent claims 21 and 27 reads on an unreasonably large number of variants which would not be expected to regenerate nerves, and for which no alternate use has been provided. Therefore, as explained above, the skilled artisan would have to determine how to use these variants, and would have to resort to undue experimentation in order to determine this.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ilag (1999. Biochemical and Biophysical Research Communications 255:104-109, of record) in view of Schwarze (1999. Science 285:1569 – 1572, of record), Voet (Biochemistry, Second Edition, 1995. pp. 58 – 59, of record), and Bertin (U.S. Patent Application Publication 2002/0061833, of record).

This rejection stands for the reasons of record. The reasons why the prior art references meet the limitations of all claims under examination are set forth in the previous office actions and for the sake of brevity will not be repeated herein. Briefly, Ilag teaches the protein of SEQ ID NO:2 and teaches it binds to the intracellular domain of p75. Schwarze teaches fusion proteins comprising PTD domains, specifically the PTD domain from HIV TAT protein and teaches the method is applicable for delivery of any protein. Schwarze even demonstrates the utility of the method in delivering beta-galactosidase, a marker protein, to the brain. Schwarze also teaches that molecules larger than 600 daltons do not enter cells.

It would have been obvious to one of ordinary skill in the art to modify the protein sequence of SEQ ID NO:2 from Ilag et al. by fusing it to the TAT PTD domain, as taught by Schwarze. The motivation to do so would be to aid the protein in crossing the cell membrane thereby inhibiting cell death. This motivation comes directly from Bertin and Voet, as Bertin teaches that proteins which bind to the intracellular domain of p75 inhibit cell death. Voet provides the weight of all twenty amino acids that are used in proteins and provides evidence that the protein of SEQ ID NO:2 (i.e. the protein from Ilag) is too large to enter the cell (note Schwarze teaches that molecules greater than 600 daltons do not enter cells), thereby motivating the artisan to modify the protein from Ilag to allow it to enter cells.

Applicant argues, at pp. 7 – 8 of the remarks, that the references fail to provide adequate motivation to make the changes to SEQ ID NO:2 that applicant has done. Applicant did not traverse the examiner's determination that every element of the claimed invention is taught by the prior art references. Applicant argues that the reference by Bertin is limited to the teachings related to CARD-3 and the CARD-3 binding domain and cannot be properly expanded to other proteins beyond CARD-3.

Applicant's arguments have been fully considered but they are not persuasive. Bertin teaches that p75 protein is known to induce death signals. See for example paragraph [0071]. This paragraph clearly identifies p75 as a receptor; the artisan of ordinary skill would immediately understand that receptors are transmembrane molecules; the extracellular domain binds to the ligand whereas the intracellular domain transduces a signal. CARD-3 is a protein that binds to this intracellular domain and inhibits cell death. As Ilag teaches another protein, that of SEQ ID NO:2, binds to the intracellular domain of p75, the artisan of ordinary skill would immediately understand that this indicates that the protein will inhibit cell death. Even if it is not conclusively demonstrated by Ilag that the protein of SEQ ID NO:2 inhibits cell death, absolute certainty is not required for a determination of obviousness, the standard is "reasonable expectation of success" (MPEP § 2143.02). Since Bertin teaches that a protein that binds to the intracellular domain inhibits cell death, the artisan of ordinary skill would reasonably conclude that other proteins that bind to the same portion of the same receptor would have the same function.

Applicant also argues, on p. 8 of the remarks, that there are other indicators of non-obviousness, particularly

1) The announcement that one of the inventors, Dr. Yamashita, had received an award "for his 'significant' and 'unexpected' accomplishments toward a cure for paralysis" is evidence of non-obviousness, and

2) The "two post-filing peer-review journal articles" provide evidence of the importance of the invention and the adoption of use by others in the field, which is also an indicium of non-obviousness.

Applicant's arguments have been fully considered but they are not persuasive. With respect to 1) above, the announcement of award fails to provide evidence of non-obviousness of the claimed invention. The document does not discuss a composition comprising the protein of SEQ ID NO:2 and a PTD domain, encompassed by the independent claims. The document does not discuss whether SEQ ID NO:2 was known in the prior art, or whether administration of same provided any unexpected results. Instead, the reference mentions that the recipients of the award "found an unexpected interaction of p75 with RhoA". While there may be a mechanistic link between the subject matter discussed in the announcement of the award and the claimed products, the announcement of award does not speak to whether or not it would

have been obvious to one of ordinary skill in the art to modify the protein disclosed by Ilag (i.e. that of SEQ ID NO:2) by attaching the well-known PTD domain of Schwarze.

With respect to 2), the post-filing reference by Yamashita (2005. Surg Cereb Stroke (Jpn) 33:395-397, submitted with the remarks filed 14 May 2007) does not provide evidence of non-obviousness of the instant invention. It is noted that the reference is in Japanese, thus it has been considered to the extent that it is understandable by someone who does not read the language. The English abstract and the Figures, some of which are annotated partly in English, do not describe a composition comprising the protein of SEQ ID NO:2 and a PTD domain, which is encompassed by independent claims 21 and 27. The reference does not provide evidence of unexpected results, which could be an indicium of non-obviousness, and does not provide evidence of adoption of the claimed invention by others, contrary to applicant's assertions.

The reference by Yamashita (2002. Journal of Cell Biology 157:565-570, submitted with the remarks filed 14 May 2007) does not provide evidence of non-obviousness of the instant invention. The reference does not describe a composition comprising the protein of SEQ ID NO:2 and a PTD domain, which is encompassed by independent claims 21 and 27. The reference does not provide evidence of unexpected results, which could be an indicium of non-obviousness, and does not provide evidence of adoption of the invention by others, contrary to applicant's assertions. Additionally, it is noted that the reference was published before the effective filing date of the instant claims. The Yamashita 2002 document was published in the issue of 13 May 2002 (see bottom of p. 565). The effective filing date of the claims under examination is 30 April 2003 as set forth above. While the reference was published the effective filing date, it is not prior art against the instant invention as it does not disclose the products now claimed.

Conclusion

9. No claim is allowed.

10. The art made of record and not relied upon is considered pertinent to applicant's disclosure: US 2007/0054848, published 8 March 2007. The reference is by the two instant inventors, among others. The reference discloses but does not claim similar subject matter. The claims in the corresponding US Patent Application (10/551157) are drawn to products comprising nucleic acid, whereas in the instant application the claims require protein, which is patentably distinct.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner

Daniel E. Kolker, Ph.D.
August 30, 2007